

Fish or Long-Chain (n-3) PUFA Intake Is Not Associated with Pancreatic Cancer Risk in a Meta-Analysis and Systematic Review^{1–3}

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Abstract

Long-chain (n-3) PUFA (LC-PUFA) have been hypothesized to be beneficial in preventing pancreatic carcinogenesis, but the associations of fish or LC-PUFA intake with pancreatic cancer found in epidemiologic studies have been controversial and inconclusive. To estimate the overall association of LC-PUFA or fish intake with pancreatic cancer, we performed a systematic literature search of English-language articles using PubMed and EMBASE through February 2012 and reviewed the reference lists from retrieved articles. Prospective cohort or case-control studies that reported ratio estimates and corresponding 95% CI for the associations of fish or LC-PUFA intake and pancreatic cancer were selected. Independent data extraction was performed by 2 of the authors. The pooled associations were obtained by using a random-effects model. A database was derived from 9 independent cohorts that included 1,209,265 participants (3082 events) with a mean follow-up of 9 y and 10 independent case-control studies that included 2514 cases and 18,779 controls. Compared with those having the lowest fish consumption, the pooled RR of pancreatic cancer was 0.98 (95% CI: 0.86, 1.12) for those who had the highest fish intake from 8 cohort studies and was 0.96 (95% CI: 0.76, 1.21) from 9 case-control studies. We found similar results for LC-PUFA intake by combining data from 4 cohorts or 2 case-control studies. Our results do not support an overall inverse association of fish or LC-PUFA intake with risk of pancreatic cancer. Further studies that consider different species and preparation methods of fish, and additional adjustment for contaminants in fish, are warranted. *J. Nutr.* 142: 1067–1073, 2012.

Introduction

Pancreatic cancer, one of the leading causes of cancer deaths among both males and females (1), has become a significant public health burden worldwide. Considering its poor prognosis and the high mortality rate, identifying factors that may prevent pancreatic cancer is of great public health interest and significance (2). Because pancreatic cancer may have an inflammatory pathogenesis (3), and long-chain (n-3) PUFA (LC-PUFA) and key nutrients in fish which include EPA 20:5 (n-3), docosapentaenoic acid [DPA 22:5 (n-3)], and DHA 22:6 (n-3), may have antiinflammatory properties (4), it has been reasonably hypothesized that fish or LC-PUFA intake may lower the risk of pancreatic cancer. A series of epidemiologic studies have examined the association of fish or LC-PUFA intake with risk of pancreatic

cancer, but findings were inconsistent and inconclusive. Some studies showed an inverse association (5–7), whereas others showed a nonsignificant association in either direction (8–22). Of note, evidence from randomized clinical trials was lacking. One meta-analysis that focused on multiple food components briefly reported the association between fish intake and pancreatic cancer by quantitatively summarizing part of the existing literature on this topic (23). The effect of LC-PUFA intake or the potential influence of fish preparation methods on pancreatic cancer risk was not addressed. For the purpose of conducting a comprehensive assessment of the overall association between fish or LC-PUFA intake and pancreatic cancer and to provide an in-depth discussion on this topic, we performed a meta-analysis and systematic review by summarizing and evaluating the relevant prospective cohort and case-control studies in the existing literature.

Methods

Data sources and searches. We identified relevant prospective cohort and case-control studies published in English-language journals that reported the categorical association between LC-PUFA or fish intake with pancreatic cancer through 15 February 2012 by searching the PubMed and EMBASE database using the terms “fish,” “seafood,” “animal product*,” “meat,” “fish oils,” “fatty acids, omega-3,” “omega-3 fatty acids,” “n-3

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³ Supplemental Text, Supplemental Figure 1 and Supplemental Tables 1–3 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

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fatty acids,” “n3 fatty acids,” “dietary fats,” and “pancreatic neoplasms,” “pancreatic cancer,” “pancreatic adenocarcinoma,” “pancreatic tumor,” “pancreatic tumors,” “pancreatic islet” and “epidemiologic studies,” and “cohort” or “case-control” (a detailed search history is provided in the Supplemental Text). We also searched the reference list from retrieved articles for more information. In addition, we included our de novo results for this meta-analysis by analyzing data from the VITamins And Lifestyle (VITAL) study (24). A review protocol is not available for this study.

Study selection. In general, articles were qualified for inclusion if they were either cohort studies or case-control studies that reported HR, OR, or other ratio estimates and corresponding 95% CI of pancreatic cancer risk relating to fish or LC-PUFA intake, or such information can be recalculated based on the available information in the primary studies. We also included cohort studies that evaluated fish intake and pancreatic cancer mortality. An unpublished study was also identified. Two reviewers (B.Q. and P.X.) independently assessed the eligibility of each study, and disagreements were resolved by group discussion. The included cohort studies involved sample sizes ranging from 61,433 to 525,473 and with participants aged ≥ 35 y. Usual fish or fish oil intake was assessed by FFQ for each study. The majority of the outcomes were confirmed by the *International Classification of Disease* (ICD) (9th or 10th revision) or *International Classification of Disease for Oncology* (ICD-O) (2nd or 3rd edition).

Data extraction and quality assessment. The data we collected included the first author’s name, year of publication, country of origin, participants’ age (range, mean, or median), proportion of men, exposure assessment, categories of fish or LC-PUFA intake, outcome confirmation, and adjusted covariates for either type of study. We also extracted data on numbers of participants and events, mean or median years of follow-up, and HR and 95% CI of pancreatic cancer for the highest consumption of fish or LC-PUFA intake versus the lowest exposure category from cohort studies, as well as numbers of cases and controls, and OR and 95% CI of pancreatic cancer from case-control studies. HR or OR were transformed to their natural logarithms (ln), and the 95% CI was used to calculate the corresponding SE. Two of the authors (B.Q. and P.X.) independently assessed each study and extracted data from eligible studies. Discrepancies were solved by group discussion.

The risk of bias in individual studies was ascertained by 2 authors (B.Q. and P.X.) based on 1) whether exposure was assessed by using a validated tool, 2) whether the case was confirmed by *International Classification of Diseases* codes, 3) whether the response rate was $>60\%$, or 4) whether the participants with other types of cancer (except for nonmelanoma skin cancer) diagnosed prior to baseline were excluded.

Data synthesis and analysis. HR and OR were our principal summary measures. We pooled HR or OR estimates from the highest and lowest categories of each study weighted by the inverse of the variance by using a random-effects model (26), and evaluated the statistical heterogeneity by calculating the I^2 statistic. Among cohort studies, we also computed the trend from the ln HR across categories of fish consumption by using the median or mean value of each category (25,26). We rescaled the unit to be a one-serving/wk increase of fish intake assuming one standard portion size of fish intake is 105 g (27). When the uppermost boundary of fish intake was open-ended, we assigned the value to be the lower bound plus the width of the closest category (28). If the fish intake among categories was unknown, we estimated the amount from studies using the same cohort and consumption categories. We used Egger’s regression asymmetry test to detect the presence of publication bias (29). We also performed sensitivity analyses to detect the potential nonlinear relation between fish intake and pancreatic cancer by replacing the highest category with other categories, and to test if the results were driven by any single study or were influenced by any identified study quality criteria. The main findings were repeated by using a fixed-effects model. We also conducted subgroup analyses in cohort studies stratified by gender (male vs. female) and the location of the study (United States vs. other countries). A 2-sided P value <0.05 was considered significant. All analyses were performed by using STATA statistical software (version 11.0; STATA Corporation).

Results

We identified 133 potentially relevant publications from our initial literature search (Supplemental Fig. 1). The database created in our meta-analysis included 8 published independent cohort studies (9–14,21,22) and one unpublished cohort study (24), which comprised 1,209,265 participants and 3082 events with a mean follow-up of 9.0 y (Table 1) and 10 independent case-control studies (5–8,15–20) with 2514 cases and 18,779 controls (Table 2). Among these, 8 cohort studies (9–14,21,24) and 9 case-control studies (5–7,15–20) reported results regarding fish consumption, whereas 4 cohort studies (10,14,22,24) and 2 case-control studies (8,30) investigated the relation between LC-PUFA intake and pancreatic cancer risk. Three cohort studies (10,14,24) presented results for both fish and LC-PUFA intake. Two case-control studies (19,30) used the same set of cases and controls to investigate the risk of pancreatic cancer with fish or LC-PUFA intake, respectively, and were counted as one independent case-control study in our pooled data set (19). The other 2 case-control studies (6,7) that shared the same set of cases were counted once in calculating the pooled case numbers.

Of the 9 cohort studies, 5 were from the United States and 4 from other countries. The number of participants ranged from 17,633 in the study by Zheng et al. (9) to 525,473 in that by Thiébaud et al. (22). Two cohorts included only female participants (11,13), and 2 included only men (9,10). The mean follow-up was 9.0 y (range: 6.3–17.4 y). All cohort studies examined fish or LC-PUFA intake by self-administered FFQ, classified into 3 to 5 categories, and reported multivariable-adjusted HR and 95% CI.

In the 10 included case-control studies, 3 were from North America, 4 from Europe, and 3 from Asia. The cases ranged from 99 in the study by Norell et al. (15) to 532 in that by Chan et al. (19). All case-control studies included both genders. Data on fish or LC-PUFA intake were collected by FFQ, 4 of which were validated. All case-control studies reported multivariable adjusted OR and 95% CI except for one study which reported 90% CI (15).

The pooled HR from 8 cohort studies that reported results on fish intake suggested that there was no significant reduction in pancreatic cancer incidence for individuals with the highest fish intake compared with those in the lowest intake category [pooled HR: 0.98 (95% CI: 0.86, 1.12); Fig. 1, Supplemental Table 1]. Similarly, the pooled HR of pancreatic cancer risk for a one-serving/wk increase in fish consumption was 0.99 (95% CI: 0.96, 1.03). We did not find significant heterogeneity among these 8 cohort studies ($I^2 = 0.0\%$, $P = 0.73$). In addition to comparing 2 extreme categories, we performed sensitivity analyses by replacing the highest category with other categories, and the results were generally consistent. None of the studies significantly influenced the summarized estimate, with pooled HR ranging from 0.95 (95% CI: 0.83, 1.10) after excluding Michaud et al. (11) to 1.05 (95% CI: 0.88, 1.26) after excluding Nöthlings et al. (12). Excluding studies with a potential risk of bias did not materially alter our findings (Supplemental Table 2; results not shown). Our results were generally consistent between the random-effects model and the fixed-effects model. The Egger’s test showed little evidence of publication bias ($P = 0.17$). The results from subgroup analysis suggested that the null association between fish consumption and pancreatic cancer risk was not modified by gender or the location of the studies (United States vs. other countries).

Similarly, the pooled results from 9 case-control studies did not show a significant association between fish intake and pancreatic cancer [pooled OR: 0.96 (95% CI: 0.76, 1.21) Fig. 2;

TABLE 1 Characteristics of 9 cohort studies included in the meta-analysis¹

First author, year (reference)	Country	No. of participants (events)	Age ² , y	Men, %	Follow-up ³ , y	Exposure assessment	Exposure categories	Outcome confirmation	Adjusted covariates
Zheng, 1993 (9)	U.S.	17,633 (57)	≥35	100	16.2	FFQ	Fish: (quartiles, times/mo) ⁴ : <0.8, 0.8–1.6, 1.7–4.0, >4.0	Death certificates, ICD-9 (code 157)	Age, smoking, alcohol, and total energy intake
Stolzenberg-Solomon, 2002 (10)	Finland	27,111 (163)	50–69	100	10.2	FFQ	Fish (quintiles, g/d): ≤17.9, 18.0–27.7, 27.8–38.6, 38.7–55.8, 55.8, fish oil (quintiles, g/d): ≤0.26, 0.27–0.35, 0.36–0.46, 0.46–0.62, >0.62	ICD-9 (code 157) excluding 157.4)	Age, smoking, and total energy intake
Michaud, 2003 (11)	U.S.	88,802 (178)	30–55	0	17.4	FFQ	Fish: <4/mo, 1/wk, ≥2/wk	Medical records or pathology reports; letter or phone call	BMI, height, smoking, total energy intake, history of diabetes, physical activity, and menopausal status.
Nöthlings, 2005 (12)	U.S.	190,545 (482)	45–75	45.3	7.4	FFQ	Fish (median of quintiles, g/1000 kcal per day): 1.1, 3.8, 6.4, 9.8, 17.3	ICD-O-2 (codes C25.0–C25.3 and C25.7–C25.9)	Age, ethnicity, smoking, total energy intake, history of diabetes, familial history of pancreatic cancer; stratified by gender and time in study
Larsson, 2006 (13)	Sweden	61,433 (172)	53.5	0	15.3	FFQ	Fish: ≤1.0/wk, 1.1 to <1.5/wk, 1.5 to <2.0/wk, ≥2.0/wk	ICD-9 (code 157) excluding 157.4)	Age, BMI, smoking, alcohol, education, total energy intake, energy-adjusted folate, red meat, processed meat, poultry, and egg
Lin, 2006 (21)	Japan	110,792 (300)	40–79	41.9	9.4	FFQ	Fish: 0–2/mo, 1–4/wk, almost every day	Death certificates, ICD-10 (code C25)	Age, smoking, and area of residence; stratified by gender
Heinen, 2009 (14)	Netherlands	120,852 (234)	55–69	48.2	13.3	FFQ	Fish (g/d): 0, 0–10, 10–20, ≥20; fish oil (median of quintiles, g/d): 0.01, 0.045, 0.08, 0.13, 0.25	Microscopy	Age, gender, BMI, smoking, alcohol, total energy intake, history of hypertension, diabetes, history of hypertension, vegetables and fruit
Thiébaud, 2009 (22)	U.S.	525,473 (1337)	50–71	58.8	6.3	FFQ	Fish oil: quintiles	ICD-O-3 (codes C25.0–C25.9, excluding histology types, 8150, 8151, 8153, 8155, 8240)	Age, BMI, smoking, total energy intake, history of diabetes; stratified by gender
He, 2011 (24)	U.S.	66,624 (159)	50–76	49.5	6.8	FFQ	Fish (tertiles, servings/d): <0.175, 0.175–0.325, ≥0.326; fish oil (tertiles, g/d): <0.123, 0.123–0.286, ≥0.287	Hospitals in the area, offices of pathologists, oncologists, radiotherapists, and state death certificates.	Age, gender, ethnicity, BMI, smoking, alcohol, education, physical activity, family history of pancreatic cancer, NSAID use, dietary intakes of fruit, vegetables, dairy products, red/processed meat, and total energy intake

¹ ICD, *International Classification of Diseases*; ICD-9, ICD 9th revision; ICD-10, ICD 10th revision; ICD-O-2, ICD for Oncology, 2nd edition; ICD-O-3, ICD-O 3rd edition; NA, not available; NSAID, nonsteroidal antiinflammatory drug; RCA, rapid case ascertainment; SEER, Surveillance, Epidemiology, and End Results.

² The mean or range of age was reported.

³ The mean or median years of follow-up were reported.

⁴ The range of fish intake was extracted from Hsing et al. (43) using the same cohort and fish consumption categories as in this article.

TABLE 2 Characteristics of 10 case-control studies included in the meta-analysis¹

First author, year (reference)	Country	Cases, <i>n</i>	Controls, <i>n</i>	Age ² , <i>y</i>	Men, %	Exposure assessment	Exposure categories	Case confirmation	Adjusted covariates
Norell, 1986 (15)	Sweden	99	138	40–79	Cases: 56	Questionnaire	Fish: more seldom, every week	Resection or autopsy (66%), radiology and biopsy (33%), or clinical and radiologic evidence (6%)	Stratified by age (2 groups), gender, and hospital/catchment area
Bueno de Mesquita, 1991 (16)	Netherlands	164	480	35–79	50	FFQ	Fish: quintiles	Microscopy (68%)	Age, gender, response status, smoking, total energy intake, low-fiber vegetables, and eggs
Mizuno, 1992 (5)	Japan	124	124 ³	40–79	55	Questionnaire	Fish: not every day, every day	Pathology, radiography, and/ or serodiagnostic analysis	Age and gender
Ji, 1995 (17)	China	451	1552	30–74	NA	FFQ	Fish (quartiles; servings/mo)—men: ≤2.6, 2.7–5.0, 5.1–9.3, ≥9.4; women: ≤2.9, 3.0–5.4, 5.5–10.9, ≥11	Histopathology (37%), surgery with gross but not microscopic pathology (20%), or computed tomography scan/ultrasound (43%)	Age, response status, smoking, income, and green tea drinking (females only); stratified by gender
Ohba, 1996 (18)	Japan	141	282 ³	64.4	60	Cases, interview; Controls, questionnaire	Fish: not every day, every day	Pathology (41.8%)	Rice, miso soup, sea weeds, natto, tofu, fried tofu, green tea, egg, green vegetables, white vegetables, fruit, mushrooms, and potatoes
Soler, 1998 (6) ⁴	Italy	362	1552 ³	Cases: 59; Controls: 55	72	Questionnaire	Fish (tertiles): low, intermediate, high	Histology	Age, gender, area of residence, education, and smoking
Fernandez, 1999 (7) ⁴	Italy	362	7990 ³	Cases: <75; Controls: 55	Cases: 63; Controls: 40	Questionnaire	Fish (servings/wk): <1, 1, ≥2	Histology	Age, gender, BMI, area of residence, education, smoking, and alcohol
Nkondjock, 2005 (8)	Canada	462	4721 ³	30–74	50	FFQ	Fish oil (median of quartiles, g/d): 0.02, 0.09, 0.18, 0.50	Histology	Age, province, educational attainment, BMI, smoking, total fat and total energy intake
Chan, 2007 (19) ⁵	U.S.	532	1701	21–85	53	FFQ	Fish (median of quartiles, servings/d): 0.1, 0.2, 0.3, 0.5; fish oil (quartiles, g/d): <0.12, 0.12–<0.22, 0.22–<0.33, ≥0.33	Physicians and SEER abstracts	Age, gender, race, BMI, education, smoking, history of diabetes, grain, vegetables and fruits, eggs, dairy, chicken and turkey, red meat, and total energy intake
Ghadirian, 2010 (20)	Canada	179	239	35–79	52	FFQ	Fish (median, μ g/d): 0, 2, 6, 24	Microscopy	Age, gender, smoking, diabetes status, proxy use, and total energy intake

¹ NA, not available; RCA, rapid case ascertainment; SEER, Surveillance, Epidemiology, and End Results.² The mean, median, or range of age was reported.³ The control was hospital-based; population-based if not specified.⁴ These 2 articles shared the same cases.⁵ Two articles shared this same cohort. One article focused on fish (19) and the other focused on fish oil (30) and were counted as one independent study.

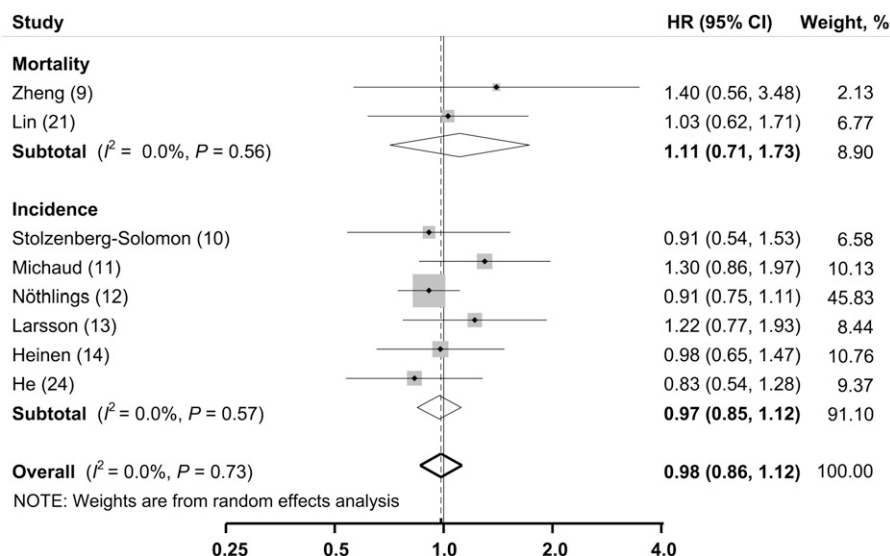


FIGURE 1 Multivariable-adjusted HR and 95% CI of pancreatic cancer risk for fish consumption (highest vs. lowest) from 8 prospective cohort studies (arranged according to study year). The pooled estimates were obtained by using a random-effects model. Dots indicate the adjusted HR of individual studies by comparing participants in the highest with those in the lowest fish consumption group. Sizes of the shaded squares are proportional to the percentage weight of each study. The diamond data markers indicate the pooled HR and 95% CI.

Supplemental Table 3]. However, the heterogeneity among these case-control studies was significant ($P = 0.001$), and 68.5% heterogeneity may be explained by the variability between studies. Nevertheless, Egger's test did not indicate the presence of publication bias ($P = 0.64$).

On the basis of the available data from either cohort or case-control studies [pooled HR: 0.90 (95% CI: 0.65, 1.26); pooled OR: 1.00 (95% CI: 0.79, 1.26)] comparing the highest intake group with the lowest, LC-PUFA intake was not associated with the risk of pancreatic cancer. The 4 cohort studies showed evidence of significant heterogeneity ($I^2 = 77.3\%$, $P = 0.004$). No strong evidence of publication bias was found among these pooled cohorts (Egger's test: $P = 0.12$).

Discussion

In this meta-analysis, which included 5596 cases of pancreatic cancer and 1,228,064 noncases from 9 prospective cohort and 10 case-control studies, we did not find an inverse association of fish or LC-PUFA consumption with risk of pancreatic cancer. Gender or study location did not modify the results.

Our results are consistent with the findings from one previous meta-analysis (23), which focused on multiple dietary components and found no relation between fish intake and pancreatic cancer from 5 independent prospective cohort studies and 3 case-control studies, and one review (31), which focused on multiple cancers and found no relation between LC-PUFA and the risk of pancreatic cancer by quantitatively combining 2 cohort studies. We performed an extensive literature search and captured more published large-cohort studies as well as case-control studies of both fish and LC-PUFA intake. Therefore, to our knowledge, our results reflect the most comprehensive and updated findings from the literature.

Most of the studies reporting the associations of fish or LC-PUFA intake with risk of pancreatic cancer were primarily designed to study either the effect of meat or dietary fat consumption. Thus, they focused on total fish rather than different species of fish or different preparation methods. This limitation might contribute to the null findings in the primary studies and this meta-analysis. Fish can be served in many ways, such as fresh, broiled, baked, salted, or fried. Fish preparation methods may alter the relation between fish intake and pancreatic cancer

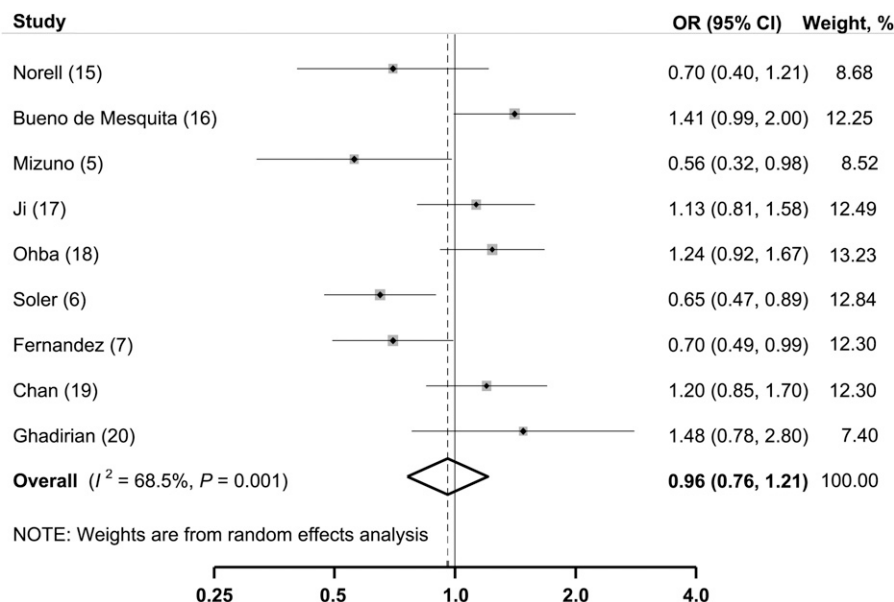


FIGURE 2 Multivariable-adjusted OR and 95% CI of pancreatic cancer risk for fish consumption (highest vs. lowest) from 9 case-control studies (arranged according to the study year). The pooled estimates were obtained by using a random-effects model. Dots indicate the adjusted OR of individual studies by comparing participants in the highest with those in the lowest fish consumption group. Sizes of the shaded squares are proportional to the percent weight of each study. The diamond data markers indicate the pooled OR and 95% CI.

by changing the lipid profile and by generating unexpected chemicals with the use of certain cooking methods. Frying, in particular, was found to considerably reduce the amount of LC-PUFA in fish (32). Deep-frying could generate *trans*-fatty acids, oxidized lipids, or food mutagens such as heterocyclic amines and benzo(a)pyrene, which may promote carcinogenesis and which was found to be associated with elevated pancreatic cancer risk (33–36). In our meta-analysis, only 2 previously published case-control studies (15,18) briefly conducted separate analyses on fish preparation methods. The case-control study by Ohba et al. (18) indicated that raw fish intake significantly reduced the risk of pancreatic cancer. The case-control study by Norell et al. (15) found that fried/grilled fish consumption may attenuate or cancel the potential benefit of fish consumption on pancreatic cancer risk. With the realization of the need for evidence on the effect of fish preparation methods as well as fish type on pancreatic cancer risk, our *de novo* cohort study conducted a relative thorough separate analysis on both fish preparation methods and fish types (24). Our results suggested that nonfried fish but not total fish intake was inversely associated with incident pancreatic cancer. Although the limited number of studies did not allow us to perform a subgroup analysis, results from the 3 studies discussed previously may indicate the beneficial effect of raw or nonfried fish on pancreatic cancer prevention. Further studies are clearly warranted to focus on the different fish preparation methods and their potentially different associations with pancreatic cancer risk.

Although LC-PUFA are believed to be the key nutrients in fish responsible for the potential benefits of fish consumption, fish is a combination of LC-PUFA and other nutrients as well as contaminants (37). The presence of mercury, dioxins, and polychlorinated biphenyls in some fish species has been a public concern because of their potential harm to human health. Because methylmercury can be readily absorbed in tissue and bioaccumulate in the aquatic food chains and food webs, larger and longer-living fish such as sword-fish may have higher tissue concentrations of methylmercury than shorter-living fish such as salmon (38). Although data in humans are currently very limited with regard to mercury exposure and cancer risk, animal studies have suggested that methylmercury may lead to kidney tumors, whereas inorganic mercuric chloride might increase the risk of several types of other tumors (39). Polychlorinated biphenyls and dioxins, believed to be carcinogenic on the basis of both animal experiments and human studies (40), are also present in fish and shellfish (38). In addition, diarrhetic shellfish poisoning toxins, a tumor agent that may accumulate in shellfish, were recently hypothesized to increase the risk of colorectal cancer (41). The finding from a large cohort study that shellfish consumption increased the risk of colorectal cancer risk was in agreement with this hypothesis (42). Therefore, combining shellfish with other fish species might also attenuate the potential beneficial effect of other nonfried fish on pancreatic cancer development. Our unpublished cohort study supported this hypothesis in which we found a moderate positive association between shellfish intake and the incidence of pancreatic cancer (39).

Overall, it might be speculated that mixing all fish species and preparation methods may have masked the potential inverse association of fish intake with pancreatic cancer risk. An extensive analysis of fish species and preparation method with pancreatic cancer risk is needed in the future.

Our meta-analysis has several merits. First, our quantitative assessment separately analyzed cohort and case-control studies. The included cohort studies comprised >1.2 million men and women with a wide age range. All of the included cohort studies had large sample sizes and long-term follow-up, which provided

high statistical power to estimate the relation between fish intake and pancreatic cancer risk. Because conducting randomized clinical trials might be impractical for prolonged compliance to the assigned amount of fish intake, meta-analyses using prospective cohort studies are considered to be a powerful tool in evaluating the long-term association between fish intake and the risk of pancreatic cancer. Second, we separately analyzed the relation of pancreatic cancer risk with fish and LC-PUFA consumption in this study. Because none of the included published studies specified that the use of fish oil supplements contributed to total LC-PUFA, dietary LC-PUFA can be viewed as a surrogate marker for fish consumption when LC-PUFA level is directly calculated from fish intake. The consistent results between fish and LC-PUFA strengthened our findings.

We performed sensitivity and subgroup analyses for cohort studies in this meta-analysis. Our results did not materially change when any single study or low-quality study was excluded. The null association between fish consumption and pancreatic cancer risk did not differ by gender or by the location of the studies. All except for one cohort study defined their cases as exocrine pancreatic cancer, which is where 95% of all pancreatic neoplasms start. Solely studying the exocrine malignancies was considered appropriate, because the etiology of pancreatic endocrine tumor may be different from that of exocrine tumor. When both univariate and multivariate models were available from one study, we selected results from maximum-controlled models.

Our study also had a few limitations. First, because the different exposure measurement scale used in the included studies and the information provided were not detailed enough to allow standardization of fish intake, our analysis primarily considered the highest versus the lowest exposure category, which prevented us from evaluating the nonlinear association. Nevertheless, the consistent finding from sensitivity analyses that replaced the highest category with other categories suggested that a U-shaped relation between fish and pancreatic cancer was unlikely. Our summarized results were subject to the limitations of any review in that the study characteristics, exposure categories, and outcome diagnosis were not the same across studies, and the inherent flaw of any observational study is that there is uncontrolled or residual confounding that might have biased the result. Although Egger's regression asymmetry test did not suggest a substantial publication bias ($P = 0.17$), a potential bias resulting from the exclusion of studies published in other languages (if any) was possible.

In summary, our meta-analysis of all relevant cohort and case-control studies indicated that there is no association between fish or fish oil consumption and the risk of pancreatic cancer. From a public health perspective, we did not find solid evidence to promote the intake of fish or fish oil supplements for pancreatic cancer prevention. However, evidence for the effect of different fish species and preparation methods on the risk of pancreatic cancer is also lacking. To fully understand the association between fish intake and pancreatic cancer, further studies that consider fish subgroups (e.g., nonfried fish, fried fish, and shellfish) and that adjust for mercury and other unhealthy constituents in fish, if possible, are required. Although evidence from this meta-analysis does not show a positive relation between fish consumption and the primary prevention of pancreatic cancer, our results should not alter the fact that fish is an overall healthy food.

Acknowledgments

K.H. designed the research; P.X. and B.Q. conducted research and analyzed data; B.Q., P.X., and K.H. drafted the manuscript

and critically revised the manuscript; and B.Q. and P.X. had primary responsibility for final content. All authors read and approved the final manuscript.

Literature Cited

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
- He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Goldbourt U, Greenland P. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke*. 2004;35:1538–42.
- Farrow B, Evers BM. Inflammation and the development of pancreatic cancer. *Surg Oncol*. 2002;10:153–69.
- He K, Liu K, Daviglus ML, Jenny NS, Mayer-Davis E, Jiang R, Steffen L, Siscovick D, Tsai M, Herrington D. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). *Am J Cardiol*. 2009;103:1238–43.
- Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Jpn J Clin Oncol*. 1992;22:286–91.
- Soler M, Chatenoud L, La Vecchia C, Franceschi S, Negri E. Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *Eur J Cancer Prev*. 1998;7:455–60.
- Fernandez E, Chatenoud L, La Vecchia C, Negri E, Franceschi S. Fish consumption and cancer risk. *Am J Clin Nutr*. 1999;70:85–90.
- Nkondjock A, Krewski D, Johnson KC, Ghadirian P. Specific fatty acid intake and the risk of pancreatic cancer in Canada. *Br J Cancer*. 2005;92:971–7.
- Zheng W, McLaughlin JK, Gridley G, Bjelke E, Schuman LM, Silverman DT, Wacholder S, Co-Chien HT, Blot WJ, Fraumeni JF Jr. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*. 1993;4:477–82.
- Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*. 2002;155:783–92.
- Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. *Am J Epidemiol*. 2003;157:1115–25.
- Nöthlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. *J Natl Cancer Inst*. 2005;97:1458–65.
- Larsson SC, Hakanson N, Permert J, Wolk A. Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. *Int J Cancer*. 2006;118:2866–70.
- Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA. Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. *Int J Cancer*. 2009;125:1118–26.
- Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, Tornberg B, Wiechel KL. Diet and pancreatic cancer: a case-control study. *Am J Epidemiol*. 1986;124:894–902.
- Bueno de Mesquita HB, Maisonneuve P, Runia S, Moerman CJ. Intake of foods and nutrients and cancer of the exocrine pancreas: a population-based case-control study in The Netherlands. *Int J Cancer*. 1991;48:540–9.
- Ji BT, Chow WH, Gridley G, McLaughlin JK, Dai Q, Wacholder S, Hatch MC, Gao YT, Fraumeni JF Jr. Dietary factors and the risk of pancreatic cancer: a case-control study in Shanghai China. *Cancer Epidemiol Biomarkers Prev*. 1995;4:885–93.
- Ohba S, Nishi M, Miyake H. Eating habits and pancreas cancer. *Int J Pancreatol*. 1996;20:37–42.
- Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control*. 2007;18:1153–67.
- Ghadirian P, Nkondjock A. Consumption of food groups and the risk of pancreatic cancer: a case-control study. *J Gastrointest Cancer*. 2010;41:121–9.
- Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Inaba Y, Kurosawa M, Kawamura T, Motohashi Y, Ishibashi T. Dietary habits and pancreatic cancer risk in a cohort of middle-aged and elderly Japanese. *Nutr Cancer*. 2006;56:40–9.
- Thiébaud AC, Jiao L, Silverman DT, Cross AJ, Thompson FE, Subar AF, Hollenbeck AR, Schatzkin A, Stolzenberg-Solomon RZ. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. *J Natl Cancer Inst*. 2009;101:1001–11.
- Paluszkievicz P, Smolinska K, Debinska I, Turski WA. Main dietary compounds and pancreatic cancer risk: the quantitative analysis of case-control and cohort studies. *Cancer Epidemiol*. 2012;36:60–7.
- He K, Xun P, Brasky TM, Gammon MD, Stevens J, White E. Types of fish consumed and fish preparation methods in relation to pancreatic cancer incidence: results from the vitamins and lifestyle (VITAL) cohort study. *Am J Epidemiol*. 2012 (in press).
- Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J*. 2006;6:40–57.
- Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to metaanalysis. *Am J Epidemiol*. 1992;135:1301–9.
- He K, Song Y, Daviglus ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation*. 2004;109:2705–11.
- Il'yasova D, Hertz-Picciotto I, Peters U, Berlin JA, Poole C. Choice of exposure scores for categorical regression in meta-analysis: a case study of a common problem. *Cancer Causes Control*. 2005;16:383–8.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–34.
- Gong Z, Holly EA, Wang F, Chan JM, Bracci PM. Intake of fatty acids and antioxidants and pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area. *Int J Cancer*. 2010;127:1893–904.
- MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM, Suttorp MJ, Lim YW, Traina SB, Hilton L, Garland R, et al. Effects of omega-3 fatty acids on cancer risk: a systematic review. *JAMA*. 2006;295:403–15.
- Echarte M, Zulet MA, Astiasaran I. Oxidation process affecting fatty acids and cholesterol in fried and roasted salmon. *J Agric Food Chem*. 2001;49:5662–7.
- Chavarro JE, Stampfer MJ, Campos H, Kurth T, Willett WC, Ma J. A prospective study of trans-fatty acid levels in blood and risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17:95–101.
- Chajès V, Thiebaut AC, Rotival M, Gauthier E, Maillard V, Boutron-Ruault MC, Joulin V, Lenoir GM, Clavel-Chapelon F. Association between serum trans-monounsaturated fatty acids and breast cancer risk in the E3N-EPIC Study. *Am J Epidemiol*. 2008;167:1312–20.
- Skog K. Cooking procedures and food mutagens: a literature review. *Food Chem Toxicol*. 1993;31:655–75.
- Li D, Day RS, Bondy ML, Sinha R, Nguyen NT, Evans DB, Abbruzzese JL, Hassan MM. Dietary mutagen exposure and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2007;16:655–61.
- He K. Fish, long-chain omega-3 polyunsaturated fatty acids and prevention of cardiovascular disease—eat fish or take fish oil supplement? *Prog Cardiovasc Dis*. 2009;52:95–114.
- Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*. 2006;296:1885–99.
- US Environmental Protection Agency. Mercury study report to Congress [cited 2011 Oct]. Available from: <http://www.epa.gov/hg/effects.htm>.
- National Center for Environmental Assessment/PCBs: cancer dose-response assessment and application to environmental mixtures. Washington, DC: Office of Research and Development, US Environmental Protection Agency; 1996.
- Manerio E, Rodas VL, Costas E, Hernandez JM. Shellfish consumption: a major risk factor for colorectal cancer. *Med Hypotheses*. 2008;70:409–12.
- Lee SA, Shu XO, Yang G, Li H, Gao YT, Zheng W. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. *Nutr Cancer*. 2009;61:194–205.
- Hsing AW, McLaughlin JK, Chow WH, Schuman LM, Co Chien HT, Gridley G, Bjelke E, Wacholder S, Blot WJ. Risk factors for colorectal cancer in a prospective study among U.S. white men. *Int J Cancer*. 1998;77:549–53.